

**BRIEF REPORT**

# The effect of stopping phenprocoumon 5 days preoperatively: A retrospective study

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**Abstract**

**Background:** Clinicians lack substantiated guidance on when vitamin K antagonist (VKA) treatment should be interrupted preoperatively, especially with regard to phenprocoumon, with its long half-life of 5.5 days.

**Objective:** To evaluate the efficacy of discontinuing phenprocoumon 5 days preoperatively and determine whether a safe international normalized ratio (INR) was reached.

**Methods:** This was a retrospective review of 118 patients using phenprocoumon prior to elective surgery. Preoperative INRs and factors that could potentially influence these values were identified and described. A safe preoperative INR was defined as <1.8.

**Results:** Of the 118 included patients, 42 patients (35.6%) had an off-target INR. The male sex was significantly and independently associated with an off-target INR (odds ratio [OR] 2.4, 95% confidence interval [CI] 1.022-5.445). A high American Society of Anesthesiologists (ASA) classification was also significantly and independently associated with an off-target INR (OR 2.3, 95% CI: 1.029-5.173).

**Conclusion:** Discontinuation of phenprocoumon 5 days preoperatively resulted in an INR < 1.8 in more than one-third of patients. Individualizing or extending the period of phenprocoumon discontinuation may be a necessary treatment option.

**KEYWORDS**

anticoagulant, international normalized ratio, phenprocoumon, preoperative care, vitamin K antagonists

**Essentials**

- There is no consensus in international guidelines regarding the preoperative discontinuation of phenprocoumon for elective surgery.
- This was a retrospective study describing 118 patients who discontinued phenprocoumon 5 days preoperatively.
- More than one-third of patients who stopped phenprocoumon 5 days preoperatively did not reach a safe INR (<1.8).
- Until prospective studies are available, we advise discontinuing phenprocoumon 7 days before elective surgery.

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## 1 | INTRODUCTION

In the opinion of the authors, stopping phenprocoumon 5 days preoperatively is often not sufficient. Too high of an international normalized ratio (INR) leads to correction with vitamin K, surgery postponement or extended hospitalization, which are associated with additional and unnecessary costs. The current Dutch guidelines recommend stopping phenprocoumon 5 days before surgery.<sup>1</sup>

## 2 | METHODS

### 2.1 | Study design and participants

A retrospective study was carried out in a nonacademic teaching hospital, Diaconessenhuis, locations Utrecht and Zeist, to evaluate the effect of discontinuing phenprocoumon 5 days preoperatively and determine the number of patients reaching a safe INR by the day of surgery.

Patients were identified by searching the hospital electronic medical records for all patients using phenprocoumon and scheduled for elective surgery between January 2010 and March 2013. Patients were excluded if it was not possible to determine the INR on the day of the intervention. All patients were advised to stop phenprocoumon 5 days preoperatively.

Patients were divided into two groups based on their INR on the day of surgery. An INR below 1.8 was considered safe; an INR greater than this value was considered a contraindication for surgery and defined as an off-target INR.<sup>2</sup> We collected the following demographic data for the participants: sex, age, therapeutic INR range, preoperative INR, American Society of Anesthesiologists (ASA) classification, and liver function disorders.<sup>3</sup> We subsequently investigated the determinants of an off-target INR.

The ASA classification system divides patients into five categories. We grouped the ASA classifications as low (I or II) or high (III or IV). ASA V patients were not included in the review.

We defined normal liver function as no current liver disease, no history of liver disease and normal liver enzyme and bilirubin levels.

### 2.2 | International normalized ratio

All INRs were analyzed using a Sysmex CA-1500 system (Kobe, Japan).

### 2.3 | Statistical analyses

Qualitative variables are expressed as the frequency and absolute percentage. These variables were compared between the groups using the chi-square test or Fisher exact test where appropriate. Quantitative variables are expressed as the mean and standard deviation. Quantitative variables were compared between the groups using the independent *t* test. Statistical significance was defined as  $P < 0.05$ .

All potential determinants of an off-target INR were investigated by univariate analyses. Missing data on the therapeutic INR range ( $n = 12$ , 10.8%) and liver function ( $n = 19$ , 16.1%) were imputed via single imputation. All variables with significant associations ( $P < 0.2$ ) in the univariate analysis were added to the binary logistic regression analysis. Odds ratios (ORs) were calculated, and the significance level was set at 0.05.

All statistical analyses were performed using the Statistical Package for the Social Sciences version 24 (SPSS, Armonk, NY, USA).

## 3 | RESULTS AND DISCUSSION

We identified 118 patients using phenprocoumon and undergoing elective surgery between January 2010 and March 2013. Forty-two patients (35.6%) had an off-target INR. These patients were more often male (73.8% male vs 53.9% female,  $P = 0.048$ ) and more often had a high ASA classification (69% high ASA classification vs 48.7% low ASA classification,  $P = 0.036$ ). The characteristics of patients with standard and off-target INRs are summarized in Table 1.

As sex and a high ASA classification were significantly associated with an INR  $< 1.8$  in univariate analyses, they were added to the binary logistic regression analysis.

Male sex was independently and significantly associated with an off-target INR (OR 2.4, 95% CI 1-5.4,  $P = 0.044$ ). To the best of our knowledge, there are no detailed studies investigating the relationship between the male sex and reduced INRs after discontinuing VKAs. This association may be due to the

**TABLE 1** Comparison of patients with on- and off-target INRs

Characteristic	INR $< 1.8$ ( $n = 78$ )	INR $\geq 1.8$ ( $n = 42$ )	<i>P</i> value
Mean age (SD)	71.9 $\pm$ 10.1	68.2 $\pm$ 11	0.63
Male, <i>n</i> (%)	41 (53.9)	31 (73.8)	0.048
Missing, <i>n</i> (%)	0 (0)	0 (0)	
Therapeutic range of INR, <i>n</i> (%)			
2-3	13 (17.1)	7 (16.7)	0.32
2.5-3.5	39 (51.3)	16 (38.1)	
3-4	17 (22.4)	14 (33.3)	
Missing	7 (9.2)	5 (11.9)	
ASA classification, <i>n</i> (%)			
Low	39 (51.3)	13 (31)	0.036
High	37 (48.7)	29 (69)	
Missing	0 (0)	0 (0)	
Liver function, <i>n</i> (%)			
Normal	50 (65)	29 (69)	0.63
Not normal	12 (15.8)	8 (19)	
Missing	8 (10.5)	2 (4.8)	

ASA, American Society of Anesthesiologists; INR, international normalized ratio; SD, standard deviation.

different diagnostic indications for starting phenprocoumon in male patients, different food consumption among male patients or poorer patient compliance.<sup>1</sup> Further research is needed to clarify this topic. In this study, we found that 43.1% and 23.9% of male and female patients, respectively, had an off-target INR. This potential risk factor is interesting; however, it is not sufficient to identify most patients with an off-target INR. A different strategy regarding phenprocoumon discontinuation may be needed for all patients.

The ASA classification was included in the binary logistic regression analysis. A high ASA classification was independently and significantly associated with an off-target INR (OR 2.3, 95% CI 1-5.2,  $P = 0.042$ ). To the best of our knowledge, no previous studies have documented the usefulness of the ASA classification in identifying preoperative patients who are at a higher risk for an off-target INR. Concomitant diseases, such as liver diseases, heart failure, malignancies, and kidney failure, are known to influence the effect of phenprocoumon.<sup>3</sup> All of the aforementioned conditions are included in the ASA classification. This seems a logical explanation for the association between a high ASA classification and an off-target INR. The advantage of the ASA classification is that it is a simple and easy classification, but it is associated with poor application consistency.<sup>4</sup> We found that 43.9% of the patients with a high ASA classification had an off-target INR compared to 25% of the patients with a low ASA classification. Again, this is an interesting finding, but in itself, it cannot be used to identify patients with an off-target INR.

The large number of patients with an off-target INR despite the discontinuation of phenprocoumon for 5 days preoperatively could be due to the long elimination half-life of 5.5 days and individual variations. It may be an option to discontinue phenprocoumon 7 days preoperatively, and in some cases, bridging therapy may be necessary. There are no detailed studies investigating this subject. The balance between the thromboembolic risk during the period of VKA discontinuation and the risk of bleeding during procedures is important. We have shown that a 5-day discontinuation period preoperatively is insufficient and therefore advise stopping phenprocoumon for at least 7 days. We are aware that no safety studies have been performed. Another possible option is to stop phenprocoumon 2 days preoperatively and start additional vitamin K treatment. It is suggested that with this management, the effect of stopping phenprocoumon is much more predictable; it prevents the dangers of bridging therapy, and the INR will increase rapidly to its therapeutic INR level postoperatively.<sup>5</sup> The safety of this strategy regarding thromboembolic events and perioperative bleeding is unknown.

The third option is using more customized guidelines. This approach requires identifying patients with risk factors for an off-target INR. Our study shows a possible association between male sex and ASA classification as risk factors. However, this method is not sufficiently accurate and requires at least prospective investigation before it is implemented in daily practice.

Our retrospective cohort study has some limitations. One limitation of our study is that the patients were advised to stop phenprocoumon 5 days preoperatively by the outpatient clinic of the preoperative screening clinic. It is possible that there was room for interpretation in the instructions regarding the timing of the last dose of phenprocoumon. This could have led to a shorter discontinuation period, which could in turn have led to an off-target preoperative INR. Second, we only included patients for whom it was possible to determine an INR on the day of the intervention, which may have led to selection bias. Nevertheless, this study shows that discontinuing phenprocoumon 5 days preoperatively is often ineffective. Third, we did not include dietary features or the use of alcohol. Due to the retrospective aspects of this study, this information could not be obtained from the medical files. The literature suggests that some dietary features and the use of alcohol could lead to changes in the INR.<sup>3,6,7</sup> Fourth, this study was not able to assess bleeding or thromboembolism outcomes. A prospective study is necessary to investigate these outcomes, and it is essential to investigate which protocol leads to an on-target INR and the fewest complications.

In summary, our findings suggest that stopping phenprocoumon 5 days prior to surgery is often insufficient to reach a safe INR preoperatively. The identified risk factors were not precise enough to establish better personalized advice. Other policies regarding stopping phenprocoumon should be investigated in a prospective study on efficacy and safety. Until a prospective study can provide better evidence, we recommend discontinuing phenprocoumon 7 days before elective surgery.

## RELATIONSHIP DISCLOSURE

The authors state that they have no conflicts of interest.

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**How to cite this article:** Knol S, Mallo M, Tromp Meesters R, Westerink J, van de Ree M. The effect of stopping phenprocoumon 5 days preoperatively: A retrospective study. *Res Pract Thromb Haemost.* 2019;3:85–88.  
<https://doi.org/10.1002/rth2.12159>